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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Beverly L. Davidson et al. Art Unit : 1648
Serial No. : 09/521,524 Examiner : Shanon A. Foley
Filed : March 8, 2000
Title : RAPID GENERATION OF RECOMBINANT ADENOVIRAL VECTORS

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF KEVIN CLARK UNDER 37 C.F.R. § 1.132

I, Kevin Clark, hereby declare as follows:

(1) That I am employed in the Library Department in the Boston office of Fish & Richardson P.C.

(2) That I contacted the publications department at Johns Hopkins University Press regarding the publication and mailing dates of the April 1999 issue of *Molecular Medicine*. They informed me that because they no longer publish *Molecular Medicine*, they were unable to provide me with any information. Johns Hopkins University Press referred me to North Shore Long Island Jewish Research Institute, the current publisher of the journal.

(3) That I attempted to contact Picower Institute Press and Springer Verlag, which apparently published the April 1999 issue of *Molecular Medicine*. As evidence of this, see the attached copy of the title page from that issue. I was unable to speak to anyone at Picower Institute Press, but I was able to get through to Springer Verlag. Springer Verlag informed me that because they no longer publish *Molecular Medicine*, they were unable to provide me with any information about the publication or mailing dates.

(4) That I spoke with Octavia Davis at North Shore-Long Island Jewish Research Institute. Ms. Davis informed me that since North Shore did not publish *Molecular Medicine* in 1999, she was unable to provide me with the date the article was first made available to the public or the date it first appeared on-line.

(5) That the Library Department at Fish & Richardson P.C. was able to obtain a copy of the cover page and the inside cover page of the April 1999 issue of *Molecular Medicine* from the Countway Library of Medicine at Harvard University. The inside cover page was date stamped by the Countway Library. The date on the inside cover page is June 15, 1999.

(6) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

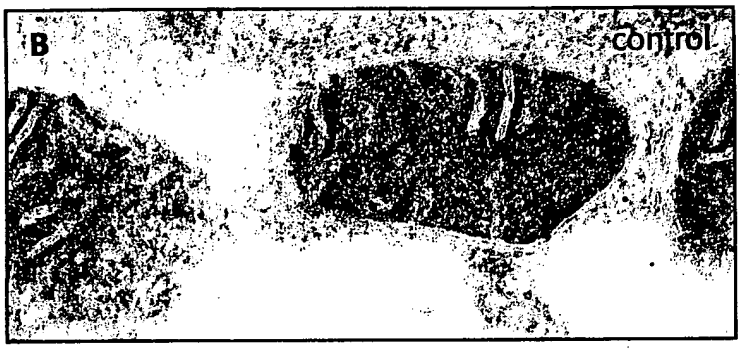
April 20, 2004
Date

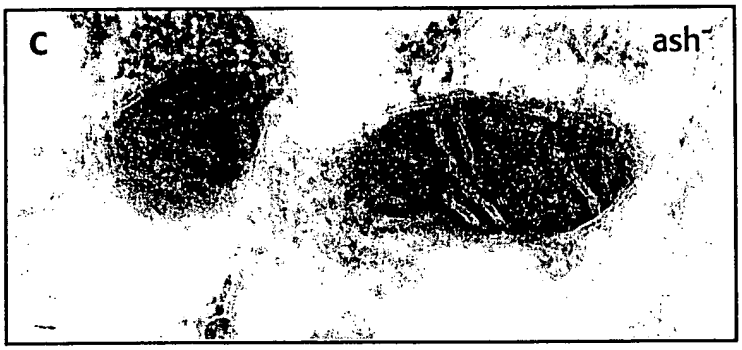
Kevin Clark
Kevin Clark

Molecular Medicine

OFFICIAL JOURNAL OF THE MOLECULAR MEDICINE SOCIETY

Volume 5 Number 4 April 1999





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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Beverly L. Davidson et al. Art Unit :
Serial No. : Examiner :
Filed : Herewith
Title : RAPID GENERATION OF RECOMBINANT ADENOVIRAL VECTORS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION BY INVENTORS UNDER 37 C.F.R. § 1.132

We, Beverly L. Davidson, Ph.D., Richard D. Anderson, Ronald E. Haskell, Ph.D., and Haibin Xia, Ph.D., hereby declare as follows:

(1) That we are co-inventors of the above-identified patent application, filed herewith, as well as U.S. Serial No. 09/521,524, which was filed March 8, 2000. The present application is a continuation of the 09/521,524 application.

(2) That Beverly Davidson, Ph.D., has been a faculty member of the University of Michigan (1990-1994) and The University of Iowa (1994-present) in Iowa City, Iowa. She currently holds the Roy J. Carver Professor Chair in Internal Medicine at The University of Iowa. In addition, she currently is the director of the Gene Transfer Vector Core at The University of Iowa. Her research involves, *inter alia*, the development of viral and non-viral vectors for gene transfer to the central nervous system. Dr. Davidson has published numerous articles in peer reviewed scientific journals in this area.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

april 20, 2004
Date of Deposit

Signature

Teresa Rogahn
Typed or Printed Name of Person Signing Certificate

(3) That Richard D. Anderson is a co-founder and currently the President of ViraQuest, Inc., in North Liberty, Iowa. Mr. Anderson obtained a B.S. from Briar Cliff College, Sioux City, Iowa in 1985 and a B.S. (CLS) from the University of Iowa College of Medicine, Iowa City, Iowa in 1986. He worked as a medical researcher at the University of Iowa from 1987 through 2001. From 1994-2001, he also supervised the Gene Transfer Vector Core facility at the University of Iowa College of Medicine. Under Mr. Anderson's supervision, the Vector Core facility produced over 300 adenoviral constructs, the subject matter of which have been published in numerous peer-reviewed scientific journals. Mr. Anderson has collaborated with Dr. Ronald E. Haskell for eight years in the generation of recombinant adenovirus.

(4) That Ronald E. Haskell, Ph.D., is a co-founder and currently the Vice President of ViraQuest, Inc., in North Liberty, Iowa. Dr. Haskell obtained his Ph.D. from Colorado State University in Fort Collins, Colorado in 1995. Dr. Haskell was employed as a Postdoctoral Fellow from 1995-1998 and as a Research Investigator from 1998-2001 in the laboratory of Dr. Beverly Davidson at The University of Iowa. During this time, Dr. Haskell performed extensive experiments using adenoviral vectors. This work has been published in five articles in peer-reviewed scientific journals. As mentioned above, Dr. Haskell has collaborated with Richard D. Anderson for eight years in the generation of recombinant adenovirus.

(5) That Haibin Xia, Ph.D. was a Postdoctoral Fellow from 1997-2000 and a Research Investigator from 2000-2001 in Dr. Beverly Davidson's laboratory at The University of Iowa. Since 2002, Dr. Xia has been an Assistant Research Scientist in Dr. Davidson's laboratory. His research involves the development of viral vectors for gene transfer to the central nervous system. Dr. Xia has published articles in peer reviewed scientific journals in this area.

(6) That we have reviewed the Aoki *et al.* reference (*Mol. Medicine* 5:224-231, 1999) cited by the Examiner in Office Actions mailed during prosecution of U.S. Serial No. 09/521,524. We make the present Declaration in support of the patentability of the claims of the U.S. patent application filed herewith.

(7) That prior to June 15, 1999, we conceived of and prepared the backbone vectors and the shuttle plasmids recited in the claims of the present application, and worked diligently to use the backbone vectors and shuttle plasmids to produce recombinant adenovirus. The conception and production of the claimed shuttle and backbone plasmids, as well as the work to produce recombinant adenovirus, occurred in the United States.

(8) That **Exhibits A through H**, attached hereto and incorporated by reference herein, are factual evidence of conception and due diligence to reduction to practice of the invention in the United States prior to June 15, 1999.

(9) That **Exhibits A through H** disclose the preparation and testing of shuttle plasmids and backbone vectors such as those recited in the claims of the attached application. As is common in research laboratories, these shuttle and backbone constructs are designated by alternate identifiers. For example, the presently claimed shuttle plasmids and backbone vectors are identified in the attached exhibits as follows:

Shuttle plasmids

Designation	*Large scale preparation*	*Alternate designation*
pAd5 RSV K-NpA	#779	Pac Ad5RSV K-NpA Ad5RSV K-NpA (PacI) pAd5RSVK-NpA(PacI) pacIAd5RSVK-NpA
pAd5 CMV K-NpA	#780	Pac Ad5CMV K-NpA Ad5cmvkNpA (PacI) pAd5CMVK-NpA(PacI) pacIAd5CMVK-Npa
Ad5 CMV hGFP		
pPACI CMV EGFP	#809	pac CMV EGFP pPACI CMV EGFP DH5alpha Ad5CMV EGFP PacI pPacICMVEGFPpA#3
Ad5 RSV hGFP		
pPACI RSV EGFP	#810	pac RSV EGFP pPACI RSV EGFP DH5alpha PacI RSV EGFP pPacIRSVEGFPpA#8 pacIAd5R$V EGFP AD5R$V EGFP

Intermediate plasmid

Designation	*Alternate designation*
del 0-1 #779 5	DELTA 0-1 779#5

Backbone plasmid

Designation	*Large scale preparation*	*Alternate designation*
del0-1sub360	#784, #849	DEL 0-1 SUB 360 #11 del0-1sub360 #3 del 0-1 sub 360 DH5alpha del sub 360 JM110 del sub 360 del0-1sub360#2 JM110

(10) That **Exhibit A** includes photocopies of three pages from the laboratory notebook of inventor Richard Anderson. While the dates on these pages have been blacked out, the original of each page is dated prior to the effective date of the Aoki *et al.* reference. These three pages refer to construction of the shuttle vectors pAd5 RSV K-NpA and pAd5 CMV K-NpA. Specifically, the first page of **Exhibit A** refers to engineering of a PacI site into the shuttle vectors, and also indicates that the vectors were prepared in large scale. The second page includes diagrams of these vectors, and also indicates the construction of the intermediate plasmid to be used in construction of the backbone. The intermediate plasmid is based on shuttle plasmid #779, but is devoid of map units 0-1 of the Ad genome. The third page indicates that the intermediate plasmid does lack map units 0-1. In addition, the third page includes a diagram of a method for making a backbone plasmid (indicated by asterisk) that lacks Adenovirus map units 0 to 9.2 and contains map units 9.2 to 100. *Thus, shuttle and backbone vectors were conceived of, and shuttle vectors were prepared, prior June 15, 1999.*

(11) That **Exhibit B** includes photocopies of two sequence chromatograms. While the dates on these chromatograms have been blacked out, the original of each page is dated prior to the effective date of the Aoki *et al.* reference. The first chromatogram shows the sequence of an intermediate plasmid that was prepared from a shuttle plasmid for use in making the backbone plasmid. The second chromatogram shows the sequence of a backbone plasmid. *Thus, shuttle, intermediate, and backbone vectors had been constructed, prepared in large scale, and sequenced prior to June 15, 1999.*

(12) That **Exhibit C** is a photocopy of a data sheet for a transfection carried out by inventor Richard Anderson, as indicated by the initials RDA entered in the space for "Initials of Transfector." While the dates on this page have been blacked out, the original page is dated prior to the effective date of the Aoki *et al.* reference. The transfection data sheet indicates that PacI-digested del 0-1sub360 #3 was used as a backbone plasmid, and the plasmids Ad5 RSV hGFP and Ad5 CMV hGFP were used as shuttles. In addition, the notes in the margin refer to the presence of green cells after the transfection, indicating that the inventors were successful in

using the cloning system to make recombinant virus. *Thus, the backbone and shuttle plasmids recited in the present claims were constructed and were used to make recombinant virus prior to June 15, 1999.*

(13) That **Exhibit D** is a photocopy of a page from the laboratory notebook of Richard Anderson. While the dates on this page have been blacked out, the original page is dated prior to the effective date of the Aoki *et al.* reference. This page refers to backbone plasmid del0-1sub360. In addition, this page indicates that inventor Ronald Haskell generated two shuttle vectors, designated pac CMV EGFP and pac RSV EGFP. Diagrams of these two vectors, which are shown to include map units 0-1 and 9.2-16 of the Ad genome, also are provided on this page. *Thus, the presently claimed shuttle and backbone plasmids were conceived of and prepared prior to June 15, 1999.*

(14) That **Exhibit E** is a printout of two pages from a spreadsheet containing information from large scale preparations of various plasmids. While the dates on these pages have been blacked out, the original pages are dated prior to the effective date of the Aoki *et al.* reference. The first page of this spreadsheet lists various shuttle plasmids, including Ad5RSV K-Npa, Ad5cmvkNpA, pPAC1 CMV EGFP, and pPAC1 RSV EGFP. In addition, this page lists the intermediate plasmid del 0-1 #779 5, and the backbone plasmid del 0-1 sub 360 DH5alpha. *Thus, a number of shuttle and backbone plasmids were prepared in large scale prior to June 15, 1999.*

(15) That **Exhibit F** is a photocopy of a seminar announcement distributed to University of Iowa faculty. The presentation was entitled "'Born to be Wild-type-Free': New Methods for Adenovirus Generations [*sic*]," and was given by inventor Richard D. Anderson. While the date on this page has been blacked out, the original announcement was printed prior the effective date of the Aoki *et al.* reference. In his presentation, inventor Anderson discussed the cloning system recited in the present claims. *Thus, the present invention was conceived of and well developed prior to June 15, 1999.*

(16) That **Exhibit G** includes photocopies of five pages from the laboratory notebook of Richard Anderson. While the dates on these pages have been blacked out, the original pages are dated prior to the effective date of the Aoki *et al.* reference. The pages in **Exhibit G** refer to a transfection using the del sub 360 backbone plasmid and the pPACI RSV EGFP DH5alpha and pPacI CMV EGFP DH5alpha shuttle plasmids. According to the first page, this transfection was carried out to make virus. The second page of this exhibit states that the transfection resulted in green cells, indicating that recombination had occurred. The third page refers to another experiment using the backbone plasmid del sub 360 and the shuttle plasmid PacI RSV EGFP. The fourth page indicates that green cells also were observed as a result of this transfection. *Thus, the cloning system as recited in the present claims was conceived of prior to publication of the Aoki et al. reference, and the inventors exhibited due diligence in reducing the invention to practice such that it was successfully used prior to June 15, 1999.*

(17) That **Exhibit H** is a print out of a three-page document summarizing the cloning system of the present invention. The document was originally prepared by inventor Richard Anderson. While the dates on this document have been blacked out, the original document is dated prior to the effective date of the Aoki *et al.* reference. The first page of **Exhibit H** discloses the method used to generate the shuttle plasmids pAd5RSVK-NpA(PacI) and pAd5CMVK-NpA(PacI), as well as the del0-1sub360 backbone plasmid. The second page provides details of the method used to generate the shuttle plasmids pPacICMVEGFPpA#3 and pPacIRSVEGFPpA#8. The second and third pages of this exhibit also disclose the method used to transfect HEK293 cells with the #810 shuttle plasmid and the del0-1sub360 backbone plasmid. *Thus, the shuttle vectors and backbone plasmids of the present invention had been prepared and used for transfection experiments prior to June 15, 1999.*

(18) We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4/08/04
Date

Beverly L. Davidson, Ph.D.

Date

Richard D. Anderson

Date

Ronald E. Haskell, Ph.D.

4-9-04
Date

Haibin Xia, Ph.D.

60207120.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Beverly L. Davidson et al. Art Unit :
Serial No. : Examiner :
Filed : Herewith
Title : RAPID GENERATION OF RECOMBINANT ADENOVIRAL VECTORS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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(2) That Beverly Davidson, Ph.D., has been a faculty member of the University of Michigan (1990-1994) and The University of Iowa (1994-present) in Iowa City, Iowa. She currently holds the Roy J. Carver Professor Chair in Internal Medicine at The University of Iowa. In addition, she currently is the director of the Gene Transfer Vector Core at The University of Iowa. Her research involves, *inter alia*, the development of viral and non-viral vectors for gene transfer to the central nervous system. Dr. Davidson has published numerous articles in peer reviewed scientific journals in this area.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

April 20, 2004
Date of Deposit

Signature

Theresa Pajeka
Typed or Printed Name of Person Signing Certificate

(3) That Richard D. Anderson is a co-founder and currently the President of ViraQuest, Inc., in North Liberty, Iowa. Mr. Anderson obtained a B.S. from Briar Cliff College, Sioux City, Iowa in 1985 and a B.S. (CLS) from the University of Iowa College of Medicine, Iowa City, Iowa in 1986. He worked as a medical researcher at the University of Iowa from 1987 through 2001. From 1994-2001, he also supervised the Gene Transfer Vector Core facility at the University of Iowa College of Medicine. Under Mr. Anderson's supervision, the Vector Core facility produced over 300 adenoviral constructs, the subject matter of which have been published in numerous peer-reviewed scientific journals. Mr. Anderson has collaborated with Dr. Ronald E. Haskell for eight years in the generation of recombinant adenovirus.

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(7) That prior to June 15, 1999, we conceived of and prepared the backbone vectors and the shuttle plasmids recited in the claims of the present application, and worked diligently to use the backbone vectors and shuttle plasmids to produce recombinant adenovirus. The conception and production of the claimed shuttle and backbone plasmids, as well as the work to produce recombinant adenovirus, occurred in the United States.

(8) That **Exhibits A through H**, attached hereto and incorporated by reference herein, are factual evidence of conception and due diligence to reduction to practice of the invention in the United States prior to June 15, 1999.

(9) That **Exhibits A through H** disclose the preparation and testing of shuttle plasmids and backbone vectors such as those recited in the claims of the attached application. As is common in research laboratories, these shuttle and backbone constructs are designated by alternate identifiers. For example, the presently claimed shuttle plasmids and backbone vectors are identified in the attached exhibits as follows:

Shuttle plasmids

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Ad5 CMV hGFP		
pPACI CMV EGFP	#809	pac CMV EGFP pPACI CMV EGFP DH5alpha Ad5CMV EGFP PacI pPacICMVEGFPpA#3
Ad5 RSV hGFP		
pPACI RSV EGFP	#810	pac RSV EGFP pPACI RSV EGFP DH5alpha PacI RSV EGFP pPacIRSVEGFPpA#8 pacIAd5R$V EGFP AD5R$V EGFP

Intermediate plasmid

Designation	*Alternate designation*
del 0-1 #779 5	DELTA 0-1 779#5

Backbone plasmid

Designation	*Large scale preparation*	*Alternate designation*
del0-1sub360	#784, #849	DEL 0-1 SUB 360 #11 del0-1sub360 #3 del 0-1 sub 360 DH5alpha del sub 360 JM110 del sub 360 del0-1sub360#2 JM110

(10) That **Exhibit A** includes photocopies of three pages from the laboratory notebook of inventor Richard Anderson. While the dates on these pages have been blacked out, the original of each page is dated prior to the effective date of the Aoki *et al.* reference. These three pages refer to construction of the shuttle vectors pAd5 RSV K-NpA and pAd5 CMV K-NpA. Specifically, the first page of **Exhibit A** refers to engineering of a PacI site into the shuttle vectors, and also indicates that the vectors were prepared in large scale. The second page includes diagrams of these vectors, and also indicates the construction of the intermediate plasmid to be used in construction of the backbone. The intermediate plasmid is based on shuttle plasmid #779, but is devoid of map units 0-1 of the Ad genome. The third page indicates that the intermediate plasmid does lack map units 0-1. In addition, the third page includes a diagram of a method for making a backbone plasmid (indicated by asterisk) that lacks Adenovirus map units 0 to 9.2 and contains map units 9.2 to 100. *Thus, shuttle and backbone vectors were conceived of, and shuttle vectors were prepared, prior June 15, 1999.*

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(12) That **Exhibit C** is a photocopy of a data sheet for a transfection carried out by inventor Richard Anderson, as indicated by the initials RDA entered in the space for "Initials of Transfector." While the dates on this page have been blacked out, the original page is dated prior to the effective date of the Aoki *et al.* reference. The transfection data sheet indicates that PacI-digested del 0-1sub360 #3 was used as a backbone plasmid, and the plasmids Ad5 RSV hGFP and Ad5 CMV hGFP were used as shuttles. In addition, the notes in the margin refer to the presence of green cells after the transfection, indicating that the inventors were successful in

using the cloning system to make recombinant virus. *Thus, the backbone and shuttle plasmids recited in the present claims were constructed and were used to make recombinant virus prior to June 15, 1999.*

(13) That **Exhibit D** is a photocopy of a page from the laboratory notebook of Richard Anderson. While the dates on this page have been blacked out, the original page is dated prior to the effective date of the Aoki *et al.* reference. This page refers to backbone plasmid del0-1sub360. In addition, this page indicates that inventor Ronald Haskell generated two shuttle vectors, designated pac CMV EGFP and pac RSV EGFP. Diagrams of these two vectors, which are shown to include map units 0-1 and 9.2-16 of the Ad genome, also are provided on this page. *Thus, the presently claimed shuttle and backbone plasmids were conceived of and prepared prior to June 15, 1999.*

(14) That **Exhibit E** is a printout of two pages from a spreadsheet containing information from large scale preparations of various plasmids. While the dates on these pages have been blacked out, the original pages are dated prior to the effective date of the Aoki *et al.* reference. The first page of this spreadsheet lists various shuttle plasmids, including Ad5RSV K-Npa, Ad5cmvkNpA, pPAC1 CMV EGFP, and pPAC1 RSV EGFP. In addition, this page lists the intermediate plasmid del 0-1 #779 5, and the backbone plasmid del 0-1 sub 360 DH5alpha. *Thus, a number of shuttle and backbone plasmids were prepared in large scale prior to June 15, 1999.*

(15) That **Exhibit F** is a photocopy of a seminar announcement distributed to University of Iowa faculty. The presentation was entitled "'Born to be Wild-type-Free': New Methods for Adenovirus Generations [*sic*]," and was given by inventor Richard D. Anderson. While the date on this page has been blacked out, the original announcement was printed prior the effective date of the Aoki *et al.* reference. In his presentation, inventor Anderson discussed the cloning system recited in the present claims. *Thus, the present invention was conceived of and well developed prior to June 15, 1999.*

(16) That **Exhibit G** includes photocopies of five pages from the laboratory notebook of Richard Anderson. While the dates on these pages have been blacked out, the original pages are dated prior to the effective date of the Aoki *et al.* reference. The pages in **Exhibit G** refer to a transfection using the del sub 360 backbone plasmid and the pPACI RSV EGFP DH5alpha and pPacI CMV EGFP DH5alpha shuttle plasmids. According to the first page, this transfection was carried out to make virus. The second page of this exhibit states that the transfection resulted in green cells, indicating that recombination had occurred. The third page refers to another experiment using the backbone plasmid del sub 360 and the shuttle plasmid PacI RSV EGFP. The fourth page indicates that green cells also were observed as a result of this transfection. *Thus, the cloning system as recited in the present claims was conceived of prior to publication of the Aoki et al. reference, and the inventors exhibited due diligence in reducing the invention to practice such that it was successfully used prior to June 15, 1999.*

(17) That **Exhibit H** is a print out of a three-page document summarizing the cloning system of the present invention. The document was originally prepared by inventor Richard Anderson. While the dates on this document have been blacked out, the original document is dated prior to the effective date of the Aoki *et al.* reference. The first page of **Exhibit H** discloses the method used to generate the shuttle plasmids pAd5RSVK-NpA(PacI) and pAd5CMVK-NpA(PacI), as well as the del0-1sub360 backbone plasmid. The second page provides details of the method used to generate the shuttle plasmids pPacICMVEGFPpA#3 and pPacIRSVEGFPpA#8. The second and third pages of this exhibit also disclose the method used to transfect HEK293 cells with the #810 shuttle plasmid and the del0-1sub360 backbone plasmid. *Thus, the shuttle vectors and backbone plasmids of the present invention had been prepared and used for transfection experiments prior to June 15, 1999.*

(18) We further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

_____
Date

Beverly L. Davidson, Ph.D.

4/6/04
Date

Richard D. Anderson

4/7/04
Date

Ronald E. Haskell, Ph.D.

_____
Date

Haibin Xia, Ph.D.

Construction of PacI site into shuttlevectors.

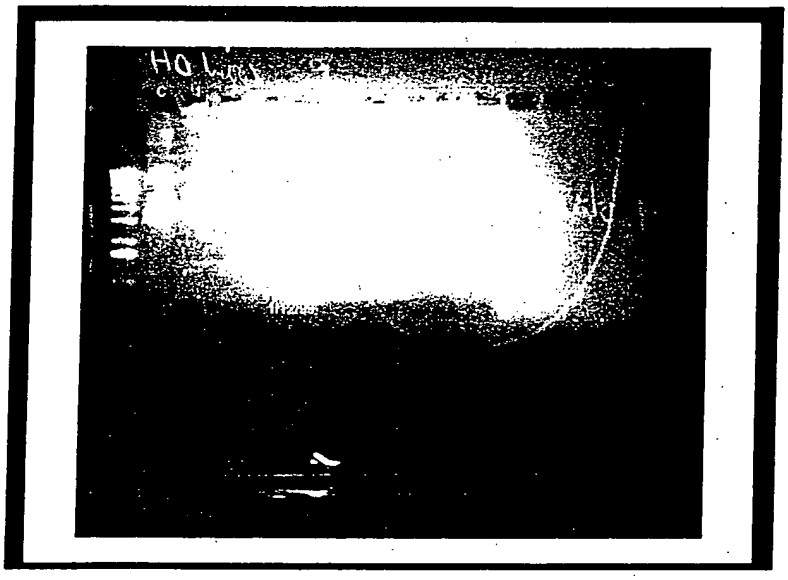
[redacted]

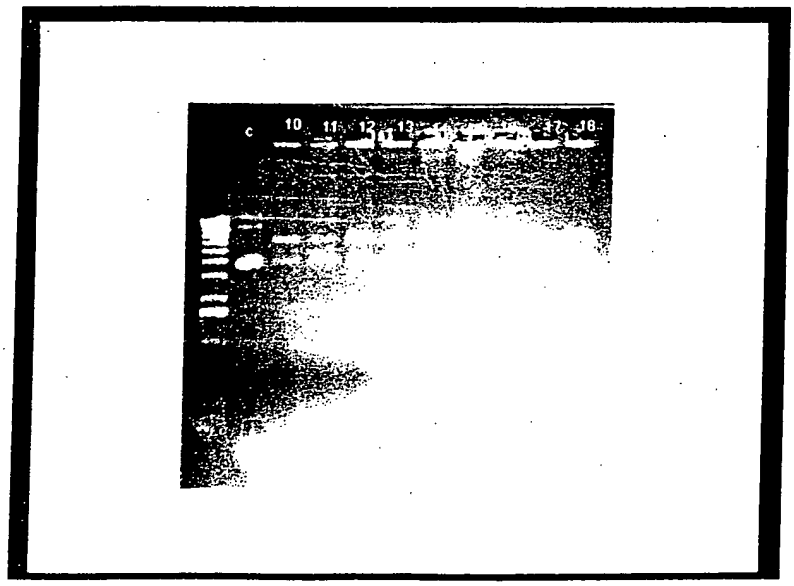
pAd5 RSV K-NpA — 2 oligos — Ad PacI for
Ad PacI rev

pAd5 cmV K-NpA

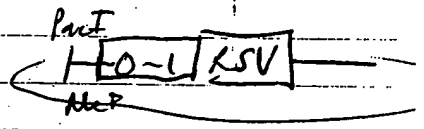
Stratagene quickchange kit by R. Haskell

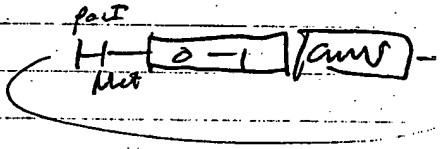
Minipreps by P. Staber
PacI digest





large scale prep of #9 #
#15 #7





* To be used for "gutless" "a" + axis

for making

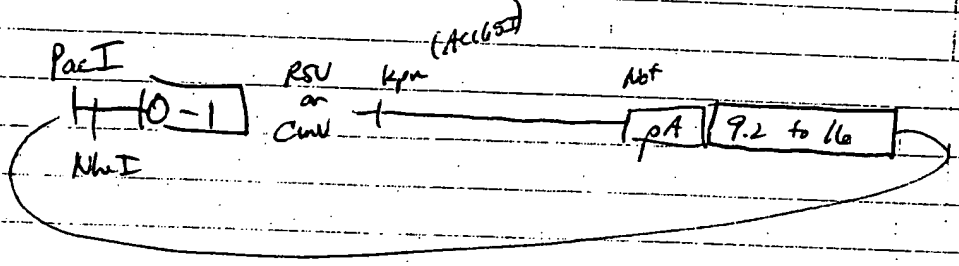
* 0-1 minus plasmid for recombinations

[redacted]

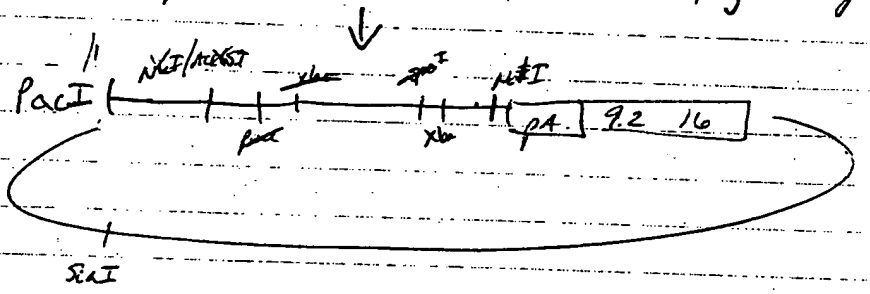
#779 Pac Ad5RSVK-Npa 0.3ug/ul

#780 Pac Ad5CMVK-Npa 0.4ug/ul

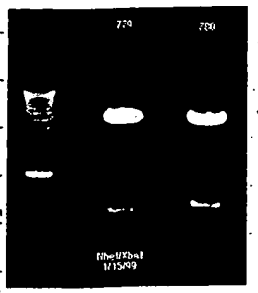
PacI digest
3ul DNA ✓
3ul 01 ✓
2ul PacI
22ul H_2O ✓



digest both ~~with~~ NheI / ~~XbaI~~ Acc65I Filter ~~T4 DNA poly~~ + ligate



NheI/XbaI will ligate together to make BstBI site



10ul #779 ✓
3ul MO ✓
1.5ul NheI
1ul Xba
14.5ul H_2O ✓

10ul #780 ✓
3ul MO ✓
1.5ul NheI
1ul Xba
14.5ul H_2O ✓

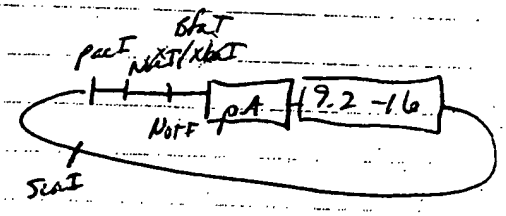
1hr 37°C

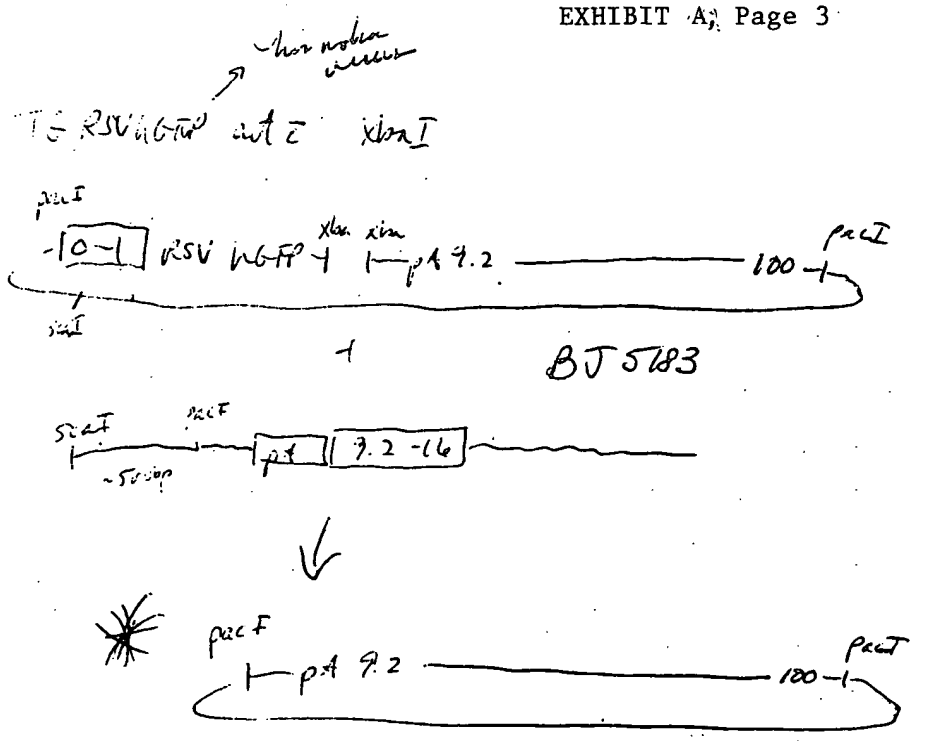
~~Isolate~~ 5ul gel ~~EtOH~~ ppt and ligate
resuspend in 20ul H_2O
add 5ul for ligation

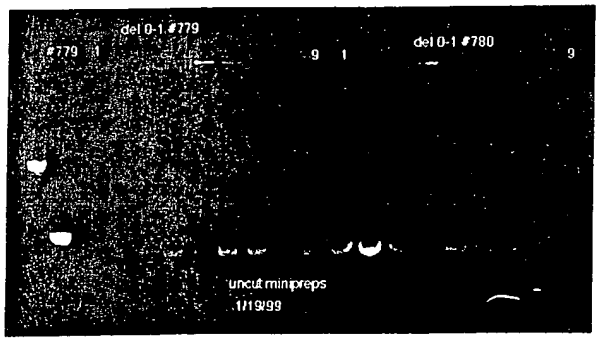
8:40am

5ul DNA
2ul 10X Lig MO
1.5ul ligase
10.5ul H_2O ✓

RT ~ 1hour







1/1

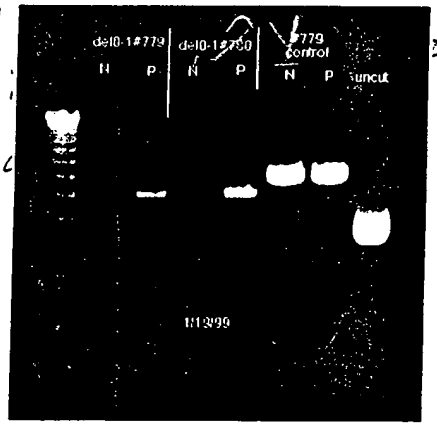
100ml DH5α + 15ul ligation

Yes. 1. #779
2. #780
3. HSVari only

-Minipreps A0-1 779 all have 1-5
A0-1 780 deletion 1-5

Sig E ARW

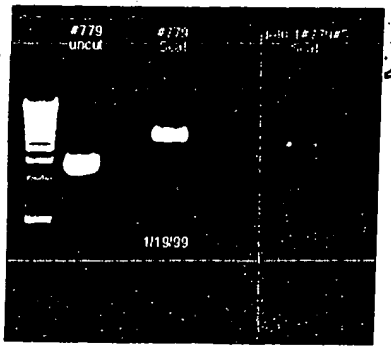
A0-1 779 #5 SalI
A0-1 780 #9



779 as control

SalI DNA
3ul 10x O
Buf Enzyme
20ul H_2O

Sig OKE
pARW.



SalI digest #9

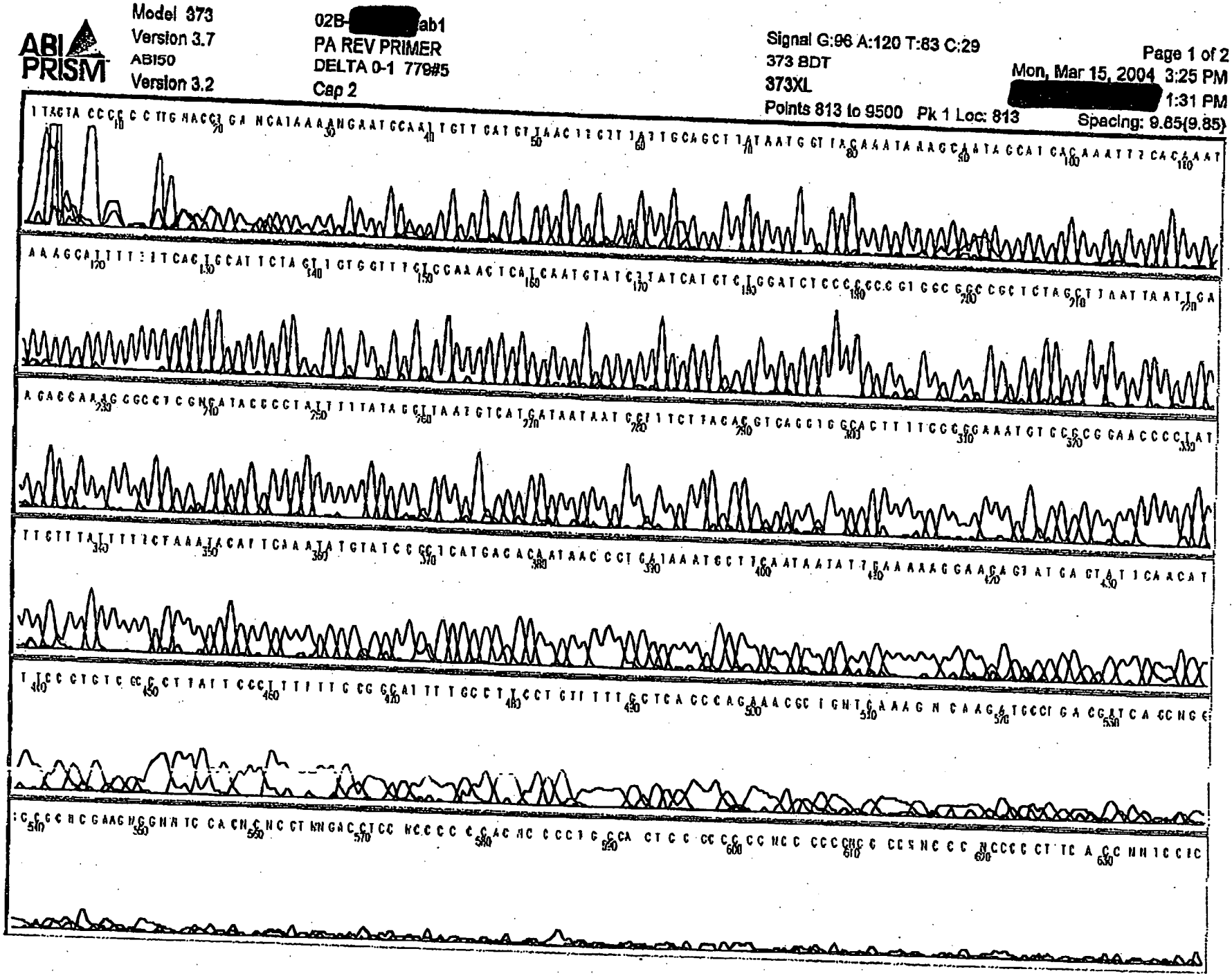


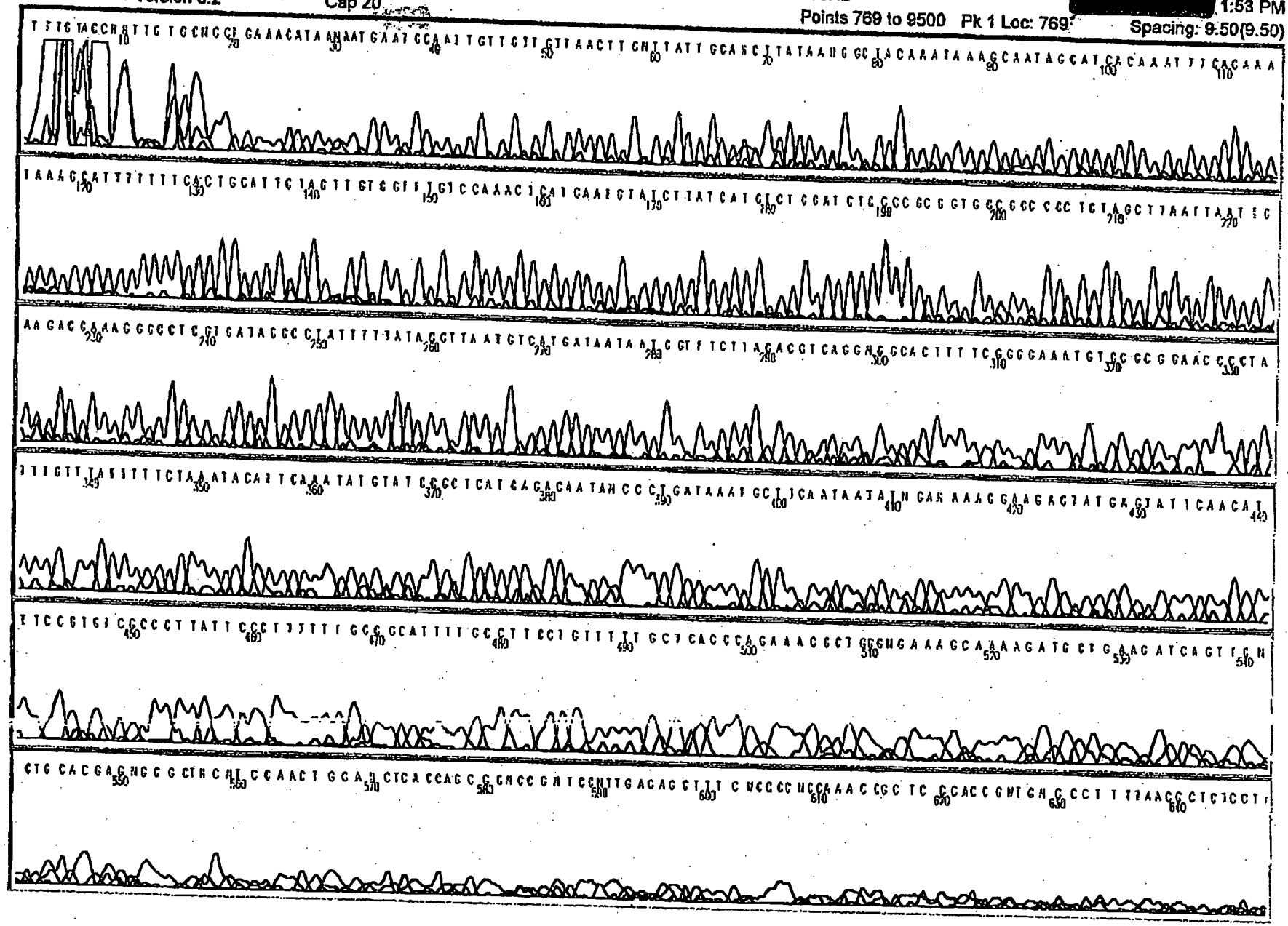
EXHIBIT B, Page 1

Model 373
Version 3.7
ABI50
Version 3.2

20B[redacted]ab1
PA REV PRIMER
DEL 0-1 SUB 360 #11
Cap 20

Signal G:82 A:95 T:64 C:27
373 BDT
373XL
Points 769 to 9500 Pk 1 Loc: 769

Mon, Mar 15, 2004 3:25 PM
[redacted] 1:53 PM
Spacing: 9.50(9.50)



Transfection for Recombinant Virus

1st del 0-1 sub 360 #3 Transfection I let go as 4 plates.

Initials of Transfector: RA

Transfection Start Date: [redacted] **Date fed:** **Date neutral red:** **Date picked:**

Shuttle plasmid	Amt used ul:	ug/ul:	Backbone:	Amt used ul:	ug/ul:	Investigator:	# plaques picked	# plaques plated
1. —	—	—	del 0-1 sub 360 #3	1ul	~1ug	GTVC		
2. Ad5RSVhGFP	10	1	PacI minprep	1ul	1ug			
3. Ad5CMVhGFP	10	1	"	1ul	1ug			
4.								
5.								
6.								
7.								
8.								
9.								
10.								

[redacted] Greenish Greenish post 24 hrs RA

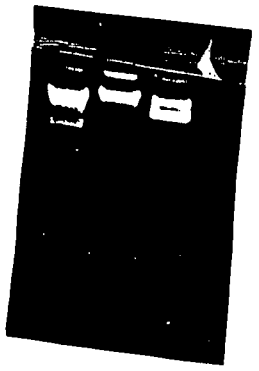
[redacted] Monolayer #a interf of green cells RA

3.5 mm

Comments:

PacI digested miniprep DNA del 0-1 sub 360 #3 ~~ppt~~ EtOH ppt resuspended in 20ul sterile H_2O used 2 previous shuttle NheI linear plasmids.

3ul *



30ul digest
100ul H_2O
5.2ul 5M NaCl
340ul 100% EtOH
10 min spin
300ul 70% EtOH wash
5 min spin
speedvac
resuspend in 20ul sterile H_2O
use 1ul.

1750ul HBSS (500ul)
1.8ul JS-DNA
3.5ul del 0-1 sub 360 #3 lipsm (1ul

500ul tubes
25ul $CaCl_2$

RT 25 min
add 2 mls 2% FBS
Add to plate.

[redacted] Removed 100ul of media added to fresh plate of 293 cells ~2:20 pm.

[redacted] cells still green and start to show "holes" in monolayer

EXHIBIT C

Restriction Digest to test plaque forming [redacted]
abilities of R+R vector Transfection old shuttles.

					6ug	10ug	10ul
PacI	1. #784	del 0-1 sc6360	0.9ug/ul	[redacted]	3ul	11ul	4ul
NheI	2. #685	pAd 5 RSV hGFP	0.3ug/ul	[redacted]	3ul	33ul	
NheI	3. #751	pAd RSV k lacZ (ut lacZ by RH)	0.6ug/ul	[redacted]	3ul	17ul	

[redacted] These need to be transfected.

Note: Ron Haskell made 2 new clones

pac CMV EGFP
pac RSV EGFP

These will be used to make virus not the above

pac NheI
+——+ 0-1 [RSV] EGFP pA 9.2-16
" " [CMV] " " " "

These will be digested w PacI or NheI to determine if either site causes problem w recombination and virus production.

Large scale preps

185	pTBE#6	2.700		R. Anderson	33883	[redacted]			PS III (-20 C) GS Box III (-80 C)
186	pTET-On#7	7.300		R. Anderson	33883				PS III (-20 C) GS Box III (-80 C)
190	psub360d^3#6	9.100		R. Anderson	33890	[redacted]			PS III (-20 C) GS Box III (-80 C)
191	psub360d^3#18	8.000		R. Anderson	33890				PS III (-20 C) GS Box III (-80 C)
215	pAd5CMV h GFP #5	1.150	2.130	RDH	33946	[redacted]	mini prep	RB	PS III (-20 C) GS Box III (-80 C)
219	SK fiblink #6	0.570	2.036	KZ/RDA	33950		mini prep		PS III (-80 C) GS Box III (-80 C)
233	pIND	6.130	2.059	Ron	1/15/1997	[redacted]		RB	PS III (-80 C) GS Box III (-80 C)
234	pIND lacZ	6.110	2.032	Ron	1/15/1997			RB	PS III (-80 C) GS Box III (-80 C)
235	pVg RXR	5.020	2.068	Ron	1/15/1997			RB	PS III (-80 C) GS Box III (-80 C)
295	AdRSV Kpn-Not	0.490	2.45	PDS/RDA	34051	[redacted]	mini prep	BA	PS IV (-20 C) GS Box IV (-80 C)
383	Ad mcs pA #9 in JM110	0.470	2.385	PDS	34158	[redacted]		BA	PS V (-20 C) GS Box V (-80 C)
384	Ad RSV K-N #5 in JM110	0.660	2.237	PDS	34158			BA	PS V (-20 C) GS Box V (-80 C)
385	Ad CMV K-N #13 in JM110	0.575	2.300	PDS	34158			BA	PS V (-20 C) GS Box V (-80 C)
491	pTG SN53	1.580	1.860	Haibin	34366	[redacted]		BA	PS VII (-20 C) GS Box VII (-80 C)
533	pTRE Ela	0.180	1.712	RDA	34429	[redacted]		BA	PS VII (-20 C) GS Box VII (-80 C)
548	Ad5.5 ires hGFP#5	0.860	1.838	RDA	34444	[redacted]		BA	PS VII (-20 C) GS Box VII (-80 C)
560	Ad5 cmVires hGFP #11	0.670	1.898	RDA	34457	[redacted]		BA/FMH	PS VII (-20 C) GS Box VII (-80 C)
598	pTGSN53E4delta#2	1.210	1.861	RDA	34493	[redacted]		FMH	pTGSN53 cut PS VII (-20 C) GS Box VIII (-80 C)
609	pTGBH1/E4delta #13	0.170	1.894	RDA	34506	[redacted]		FMH	PS VII (-20 C) GS Box VIII (-80 C)
616	pTGSN53/swaI	1.400	1.830	Haibin	34515	[redacted]		FMH	PS VII (-20 C) GS Box VIII (-80 C)
621	pTGBH1/SWaI-1	0.450	1.799	Haibin	34522	[redacted]		FMH	PS VII (-20 C) GS Box VIII (-80 C)
622	pTGBH1/SWaI-2	0.450	1.817	Haibin	34522			FMH	PS VII (-20 C) GS Box VIII (-80 C)
638	pTG3602/SwaI	0.270	1.765	Haibin	34541	[redacted]		FMH	PS VII (-20 C) GS Box VIII (-80 C)
651	Ad5RSV CEB	0.670	1.727	RDA	34563	[redacted]		FMH	PS VII (-20 C) GS Box VIII (-80 C)
661	pTG360	0.290	1.611	Haibin	34577	[redacted]		FMH	PS VII (-20 C) GS Box VIII (-80 C)
779	Ad5RSV K-NpA (PacI) #9	0.330		1.941 RDA	34710	[redacted]		FMH	PS VII (-20 C) GS Box X (-80 C)
780	Ad5cmvkNpA (PacI) #15	0.370	>2.00	RDA	34710			FMH	PS VII (-20 C) GS Box X (-80 C)
784	del 0-1 sub 360 DH5alpha	0.880		1.832 RDA	34726	[redacted]		FMH	PS VII (-20 C) GS Box X (-80 C)
796	del 0-1 #779 5	0.450		1.917 RDA	34743	[redacted]		FMH	PS VII (-20 C) GS Box X (-80 C)
809	pPAC1 CMV EGFP	0.470		1.879 Ron	34756	[redacted]		FMH	
810	pPAC1 RSV EGFP	0.540		1.876 Ron	34756			FMH	

EXHIBIT E, Page 1

87xxbp, pTG1696 not2, Spe2 cut then ligate

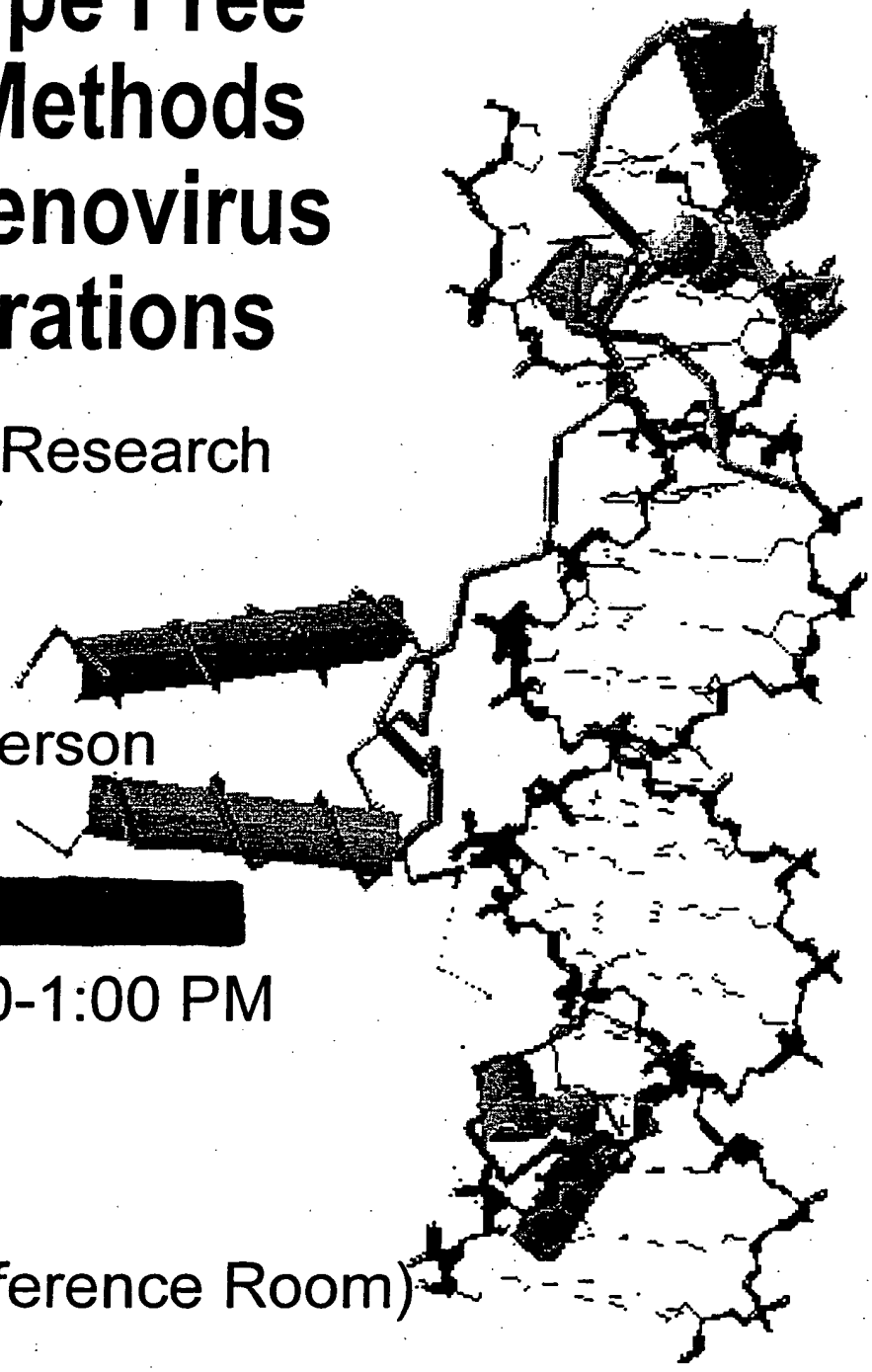
Ad5 wt with Kpn1 religated p35 lacZ to use for new ires hGFP vector

5mal delted E4 E.coli reombined with pTGBH1

Pac I restriction site @ bp 1 of shuttle vector
Pac I restrestriction site @ bp 1 of suttle vector

EXHIBIT F

"Born to be Wild-type Free" New Methods for Adenovirus Generations



Gene Transfer Research Group Seminar

Presenter:

Richard D. Anderson

[redacted]

12:00-1:00 PM

1-561 BSB

(MacEwen Conference Room)

Lunch will be provided

Transfection to make virus from 2 plasmids

Backbone #849 dl/sub360 JM110 @ .2 ug/ul

shuttle #810 pPACI RSVEGFP DH5α 0.5 ug/ul

shuttle #809 pPACI CMVEGFP DH5α 0.5 ug/ul

10 ug of shuttle plus 1 ug backbone

digested w PacI for 1 hour

Then Ca(PO4) ppt into 293 cells let go for

3 days then harvest.

2 ul shuttle	10 ul Backbone
3 ul 10xO	3 ul 10xO
2 ul PacI	2 ul PacI
5 ul H_2O	15 ul H_2O

37°C 1 hour.

Ron took pictures 810, 809 + 849 showed an increase in the # of green cells after 72 hrs.

Talked to Hiabin and he thought 3 days maybe to early based on his E-coli virus production

There appeared to be cpe and plates were harvested at 72 hrs frozen thawed x3 and placed on A549 cells No green after 24 hours.

Repeat and wait for complete cpe ~ 5-7 days.

plates used >80% confluent
Ca#P left on for only ~2 hours
before changing media.

pictures in Steve R&R folder under
R+R heading.

[redacted] #809 + R+R lysate on 293 cells shows 3
green cells Today.

First evidence of recombination by this
method.

Ran put lysate on Tues a.m. Took pictures there were a total of 6 green cells will add fresh media to plates and look over the weekend.

[redacted] Added 2mls fresh 10% FBS/DMEM.

R+R recombination in 293 cells

#849 del sub 360 0.2 ug/ul 20 ul = 4 ug

#810 Pac I KSV Eggs 0.54 ug/ul 8/2/99 ~18.5 ul ~10 u

5 ul 10x O
2 ul Pac I
5 ul H_2O
37°C 1 hour.

Heat kill 65°C 20 min use in transfection

60 mm plate 293
1 #849 only
2 849 plus 810

Ad CMV TLR 2 #3 (Zehner) cut ε Nhe I

Transfected ε subcloned viral DNA

PSV EGFP

#810

pretty good transfection ~ #809/R$R [redacted]

" cells look healthy will take picture and follow over the weekend to watch for increase in "green".

pictures in R$R folder [redacted] labeled @ ~24hrs

[redacted] pictures on Davidson Server for 48 hrs.
72 hrs
4 days
5 days
6 days
7 days

[redacted] increase in "green" cell number and different intensities of "green"

# of cells appears to increase til day 4.

at day 5 not much difference. day 6 great looking ones very infected green cells without a center (plaque) with a trailing of lighter green cells behind it.

[redacted] removed 200ul of media from #7 plate on [redacted] added it to 100mm plate 293 cells ~ 60% confluent.

a.m. looked at plate briefly and saw green cells!! should be due to viral infection media from the R$R system plate #7

2:00pm 4-6 "comets" on the 100mm plate very clearly virally infected 293 cells that are expressing EGFP.

harvest plate #7 on [redacted] to make lysate for particle amplification. let 100mm go until CPE

Restriction Digest to produce Recombinant Adenovirus using R&R system

adenoplast	1. Ad5CMV flut4-eGFP	NheI cut	1ug/ul	Persin
dH2O 8ul	2. Ad5CMV MSR A #6	NheI cut	~1ug/ul	Hoshi
dH2O 19ul	3. Ad5CMV SC1CN3/GFP #813	NheI cut	~1ug/ul	Lamb.
5ul 10x O	4. Ad5CMV EGFP pacI			
2ul NheI				

(x2) #349 del Sub 360 0.2ug/ul 20ul
3ul 10x
2ul pacI
5ul H_2O

#23 outside DNA sample - 20
Rm 221

500 µl HBS O
shuttle plasmid
R&R backbone
vortex
25ul $CaCl_2$
vortex
RT 25min
Add to 2mls 2% FBS/DMEM 2-4 hours
Change media to 4mls 10% FBS/DMEM

let go ~7days.

Watch GFP virions for increase in green after 3 days.

R$R Adenovirus Recombination System

Shuttle vector construction:

pAd5CMVK-NpA#390 and pAd5RSVK-NpA#600 were used for the starting plasmids for the system. The EcoRI site of these shuttles was converted to a PacI site by the Quik change™ site directed mutagenesis kit from Stratgene.

The primers used or this are as follows:

AdPacIfor 5'-AGGCCCTTTCGTCTTCAA**TTAATTAA**GCTAGCATCATCAATA-3'

AdPacIrev 5'-TATTGATGATTGCTAGC**TTAATTAATT**GAAGACGAAAGGCC-3'

Bold letters are the PacI restriction site underlines are the NheI site.

Quikchange carried out by Dr. Ron Haskell plasmids grown and CsCl purified:

#779 pAd5RSVK-NpA(PacI) [redacted]
#780 pAd5CMVK-NpA(PacI) [redacted]

Production of deleted 0-1 map unit shuttles:

#779 and #780 digested with NheI and XbaI and re ligated on itself. This removes the 0-1 m.u. of the Ad5 genome that contains the left hand ITR and packaging signal. It also removes the promoter region RSVor CMV.

Only continued with one of these new plasmids from the #779 re ligation. The new shuttle is called del0-1#779#5 changed to del0-19.2-16. This plasmid was sequenced with the pArev primer(5'-TTAAAAAACCTCCCCACCTCCCCC-3') 02B-[redacted].

To make the R$R backbone(del0-1sub360) the following plasmids were used:

pTGRSVhGFP This plasmid was produced by Lane Law by the E.coli recombination system from Transgene. pTG3601 was digested with Bgl II and co transformed into BJ5183 E.coli with pure viral DNA from Ad5RSVhGFP adenovirus particles. Colonies were screened by EcoRI restriction digest and the correct plasmid purified on CsCl gradient.

The del0-1backbone was created by using the E.coli system to delete the 0-1m.u.RSV promoter and the hGFP gene as follows. The pTGRSVhGFP was digested with XbaI and the del0-1 9.2-16 shuttle was digested with ScaI both of these plasmids were transformed into BJ5183 E.coli and minipreps isolated. del0-1sub360#11 from the BJ5183 E.coli was sequenced with the pArev primer 20B-[redacted]. This DNA was them transformed into DH5α E.coli and CsCl purified#784(methylated). Upon checking this plasmid by restriction digest with EcoRI it appeared there was a mutation at this site that should have been at position 30009bp of the Ad genome. Plasmid #784 was sequenced with E3for2 primer(5'-

GTCCAACTACAGCGACCCACCCTAACAGAG-3') 11W-[redacted] the sequence aligned with Ad5 dl309 sequence which is correct.

#784 was re transformed into JM110 E.coli [redacted] failed to give colonies at 37°C for 2 minutes during heat shock step of transformation. #784 plasmid was transfected into HEK293 cells cells were harvested 24 hours later and run on a western blot [redacted]. Lysates tested versus 4D2.5 fiber monoclonal and Sheep90 adenovirus polyclonal. Lysates from #784 gave positive band for fiber and had a similiar pattern for the sheep polyclonal as compared to purified virus particles. E.coli transformation into JM110 was repeated using 2 minutes at 42°C, as per suggestion of Dr. Hiabin Xia, during the heat shock step. Isolated 2 colonies and grew a large scale prep of del0-1sub360#2 JM110 changed name to del0-1sub360[R$R backbone #849[redacted]].

First Adenovirus recombination in HEK293 cells was carried out to make Ad5R$V EGFP. The shuttle used for this virus was constructed as follows:

pacIAd5RSVK-NpA#779 and pacIAd5CMVK-NpA#780 were digested with XhoI/NotI and ligated to the XhoI/NotI fragment from Clonetech pEGFP-N1 accession# U55762 (cat.#6085-1). Minipreps were checked with SalI restriciton digest. Large scale CsCl DNA was made from the positive clones pPacICMVEGFPpA#3 (#809)and pPacIRSVEGFPpA#8 (#810).

10μg of pacIAd5R$V EGFP#810[redacted] was digested in a 30μL reaction using 8 units of PacI restriction enzyme at 37°C for 1 hour. The PacI was then heat killed at 65°C for 20 minutes. Two micrograms of R$R backbone #849 was digested as above[redacted].

HEK293 cells were plated at ~1.5x10^6 cells per 60mm plate 24 hours pre-transfection in 10% FBS/DMEM P/S and incubated in 95% humidity 5% CO_2. The transfection protocol was carried out as per the traditional Ca^{++} Phosphate method used in the Gene Transfer Vector Core. The R$R backbone and the Ad5R$V EGFP shuttle were added to 500 μL of HEBS buffer pH 7.1 and breifly vortexed. 25 μL of 2.5 M $CaCl_2$ was added to the tube and precipitant allowed to form at room temperature for 25 minutes. During this time period the media was changed on the transfection plate to 2% FBS/DMEM and placed in the incubator to equilibrate. The total preciptant was added drop wise to the 2 mLs of media. The transfection media was left on the cells for ~2.5-3 hours before changingto 10% FBS/DMEM and allowed to incubate for ~ 7 days. The number of green cells was monitored by fluorscence every 24 hours. At day 6[redacted] 200 μL of media was removed and added to a 50% confluent plate of HEK293 cells in a 100mm plate. Green cells were observed after 24 hours and cpe seen after 48 hours post infection with the 200 μL of media.

10 150mm plates of HEK293 cells were plated at 2 x10^6 cells per plate 3 days before infection with the media and cell lysate of the Ad5R$V EGFP trnafection plate. The infection was allowed to go for ~ 30 hours before harvesting. The infected cells were spun in a 50 mL Falcon tube and the media aspirated. The cell pellet was washed one time with 1x PBS and resuspended in 0.5 mL of 10 mM Tris pH 8.0 per plate collect. The cell suspension was freezed thawed 3 times in an ethanol dry ice bath and the cell lysate collected. The lysate was then passed over a CsCl gradient and the virus particles isolated. The new Ad5R$V EGFP particles[redacted] were resuspended in an equal volume of 50% glycerol/1% BSA and stored at -20°C.

Viral DNA was isolated from 100 µL of the Ad5R$V EGFP particles [redacted] and PCR was carried out to determine the prescence of "wild-type" E1 positive signal. The viral particles were incubated with an equal volume of 2x Pronase solution at 37°C for at least one hour. The sample was then phenol/Chloroformed extracted, NaCl2/EtOH precipitated and resuspended in 100 µL H_2O. 5 µL(~3.5 x10^10 genomes) of this was used in a 50 µL PCR reaction using E1for2/E1rev1 and E3for2/E3rev1 primers.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Beverly L. Davidson et al. Art Unit : 1648
Serial No. : 09/521,524 Examiner : Shanon A. Foley
Filed : March 8, 2000
Title : RAPID GENERATION OF RECOMBINANT ADENOVIRAL VECTORS

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF ELIZABETH N. KAYTOR, PH.D. UNDER 37 C.F.R. § 1.132

I, Elizabeth N. Kaytor, hereby declare as follows:

(1) That I am employed as a Technology Specialist in the Minneapolis office of Fish & Richardson P.C., P.A.

(2) That I obtained the April 1999 issue of *Molecular Medicine* from the Bio-Medical Library at the University of Minnesota in Minneapolis. A copy of the cover page of the April 1999 issue is attached. The cover page is date stamped June 15, 1999.

(3) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

April 20, 2004
Date

Elizabeth N. Kaytor
Elizabeth N. Kaytor, Ph.D.

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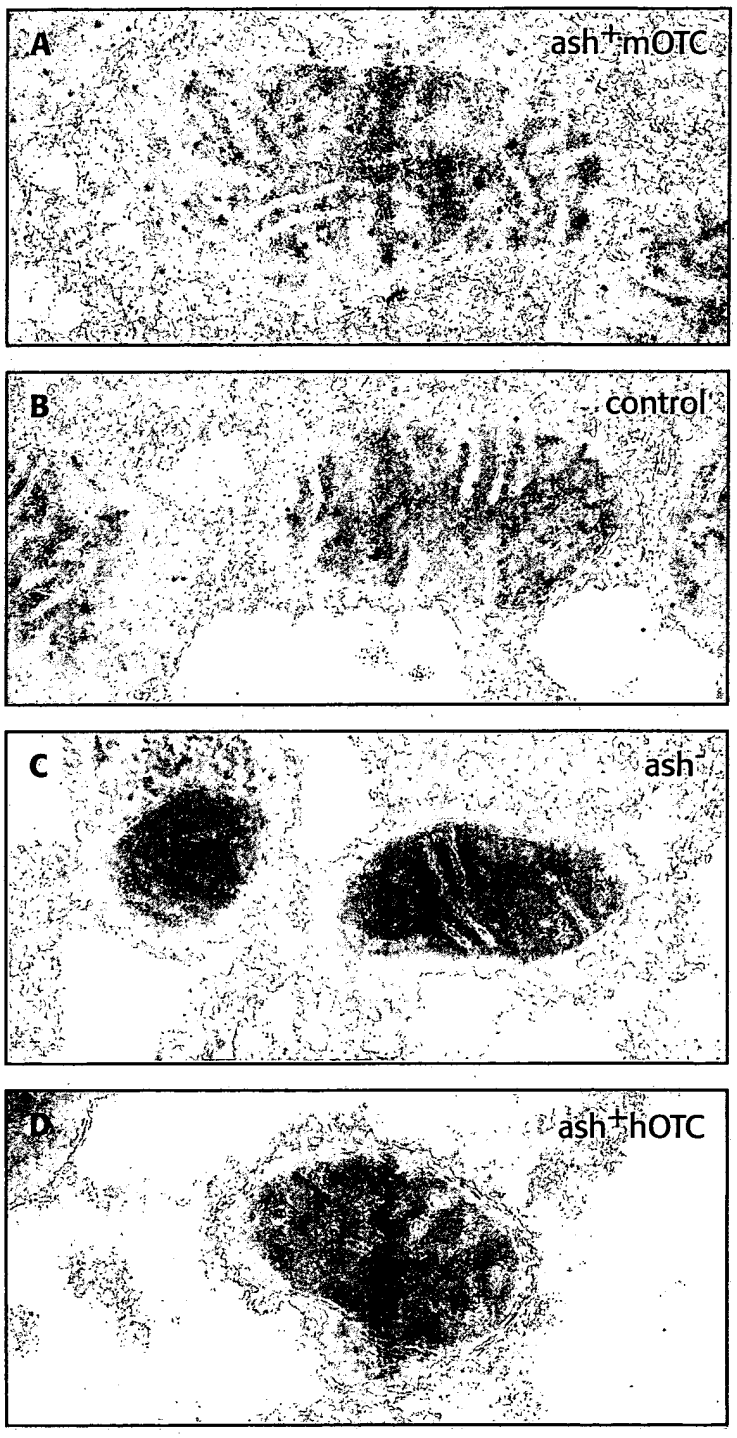

OTC labeling

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EDITORS

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Cover: Ultrathin frozen liver sections from a spf^{ash} mouse treated with Ad.mOTC (A), control C3H mouse (B), untreated spf^{ash} mouse (C), and spf^{ash} mouse treated with Ad.hOTC (D). Labeled with rabbit anti-OTC antibody followed by gold-conjugated goat anti-rabbit antisera. Representative mitochondria are shown from each mouse. See article by Zimmer et al. on page 244 in this issue.

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